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Retinal morphology and function in prematurely-born children at school age.

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Abstract

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Preterm birth may lead to complications during the neonatal period that can cause visual dysfunctions. Retinopathy of prematurity (ROP) and neurological complications are well known reasons for visual dysfunctions, but preterm children with no or only mild ROP and no evident neurological problems may also be affected visually when they grow up. Retinal development starts early after gestation and continues long after birth. Major processes are underway during the second half of pregnancy when preterm children are born, and a preterm birth could possibly have a negative effect on normal retinal development.

The aims of the studies were to evaluate retinal morphology and function in former preterm children and compare the results with children born at term.

Former preterm children aged 5 to 17 years and born in a gestational age (GA) of 32 weeks or less were included in the different study groups. Children of similar ages who were born at term and with normal visual acuity (VA) acted as controls. Best corrected VA and refraction in cycloplegia were assessed in all children. Macular thickness and retinal nerve fiber layer (RNFL) thickness were measured with optical coherent tomography (OCT). Total retinal function was assessed with fullfield electroretinography (ffERG) and central macular function was assessed with multifocal electroretinography (mfERG).

Preterm children had thicker central maculae than controls. There was a positive correlation between central macular thickness and GA at birth. RNFL thickness was reduced in the preterm children with severe ROP and treated ROP, but children with mild or no ROP did not differ from the fullterm children. The photoreceptor function measured with ffERG and the macular function measured with mfERG were reduced in the preterm group compared to controls.

Preterm birth affects the retina both morphologically and functionally, and ROP has been suggested to be a reason for retinal changes. However, the results of this thesis indicate that children with no ROP also have retinal changes, suggesting an effect of prematurity itself. There were no correlations between any retinal changes and VA, but it is possible that larger studies using improved techniques may elucidate this further.

Keywords: Retinopathy of prematurity, Prematurity, Retinal development, OCT, Fullfield ERG, Multifocal ERG

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To my family

...there is something you must always remember. You are braver than you believe, stronger than you seem, and smarter than you think...

Christopher Robin to Winnie the Pooh

List of Papers

This thesis is based on the following studies, which are referred to in the text by their Roman numerals.

- I Åkerblom H, Larsson E, Eriksson U, Holmström G. Central macular thickness is correlated with gestational age at birth in prematurely-born children. *Br J Ophthalmol* 2011;95:799-803.
- II Åkerblom H, Holmström G, Eriksson U, Larsson E. Retinal nerve fiber layer thickness in school-aged prematurely-born children compared to children born at term. *Br J Ophthalmol* 2012;96:956-60.
- III Åkerblom H, Andreasson S, Larsson E, Holmström G. Photo-receptor function in school-aged children is affected by preterm birth. *Transl Vis Sci Technol.* 2014;3:7.
- IV Åkerblom H, Andreasson S, Holmström G. Macular function in preterm children at school age. In manuscript.

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Abbreviations

BW	Birth weight
FfERG	Fullfield electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
GA	Gestational age
IVH	Intraventricular hemorrhage
MfERG	Multifocal electroretinography
OCT	Optical coherent tomography
PRP	Panretinal photocoagulation
PVL	Periventricular leucomalacia
RNFL	Retinal nerve fiber layer
ROP	Retinopathy of prematurity
SD-OCT	Spectral domain optical coherent tomography
TD-OCT	Time domain optical coherent tomography
VA	Visual acuity

Introduction

In northern European countries 5% of all infants are born prematurely, i.e. before 37 weeks of gestation (Blencowe et al., 2013). The number of children, who survive, especially the most premature, has increased due to improved ante- and neonatal care (Battin et al., 2012). When growing up, this group of children has been reported to have problems concerning cognitive abilities, learning abilities, motor skills, hearing and vision (Johnson et al., 2009).

Former preterm children are at greater risk of various visual dysfunctions when they get older, compared to children born at term (Holmstrom & Larsson, 2008; O'Connor et al., 2004). The main risk factors are retinopathy of prematurity (ROP) and neurological complications during the neonatal period (Hellgren et al., 2007). It has, however, been shown that children with only mild or no ROP and no known neurological problems may also have visual problems (Holmstrom & Larsson, 2008). Retinal development takes place chiefly during the second part of pregnancy and consequently preterm birth might lead to a disturbance in the normal development of the retina and optical pathways, which could explain some of the visual dysfunctions.

The present thesis includes four studies of retinal morphology and function in former preterm children compared to healthy children born at term. Optical coherent tomography (OCT) is a technique that provides cross sectional images of the retina in the macular region as well as the retinal nerve fiber layer (RNFL) around the optic nerve head. Fullfield electroretinography (ffERG) and multifocal electroretinography (mfERG) provide information concerning the total retinal function and the localized function of the macular region, respectively. Together, these three techniques can provide detailed information about how the retina in a prematurely-born child differs from that in a child born at term.

Background

Prematurity

Preterm birth is a significant health problem worldwide (Beck et al., 2010). Approximately 5-7% of live births are premature (children born before 37 weeks of gestation) and the incidence is rising, especially in developing countries. Advances in ante- and neonatal care, such as the use of antenatal steroids, surfactant replacement treatment and improved respiratory support, have resulted in increased survival of the most preterm children (Battin et al., 2012). A national study of infants with a gestational age (GA) of 27 weeks or less and born between 2004 and 2007 in Sweden, reported a one-year survival of 70% (ExpressGroup, 2010). More than half of the children surviving their first year had major complications due to their prematurity, including intraventricular hemorrhage (IVH), periventricular leucomalacia (PVL) and severe ROP. The complications led to various problems for these children later in life and at 2.5 years of age 58% of the children had mild to severe neurodevelopmental disabilities, including cognitive and language difficulties, impairment of motor functions, hearing and vision (Holmstrom et al., 2014a; Serenius et al., 2013). It has been suggested that a delay in general maturation in the prematurely-born children could explain some of these effects, but in other studies focusing on older children the higher risk for neurodevelopmental disabilities remains when comparing them with children born at term (Johnson et al., 2009). The increased number of pre-term births together with improved neonatal care creates a growing group of children with long-term health issues caused by the preterm birth.

Retinopathy of prematurity

ROP is a retinal disease affecting children born prematurely that was first described in 1942 (Terry, 1942). The pathophysiology of ROP is still not completely known but a two-phased process has been suggested (Smith, 2004). The retinal vessels are not fully developed when children are born preterm. The environment outside the uterus is more hyperoxic compared to in utero, and since preterm children lack the ability to autoregulate their blood flow, a retinal hyperoxia will develop. The hyperoxia leads to a down

regulation of growth factors, which inhibits the growth of the retinal vessels in the first phase of the disease. The result is an obliteration of the retinal vessels, thereby leading to hypoxia. In the second phase of the disease, this hypoxia triggers an upregulation of growth factors, which may lead to neo-vascularization, vessel growth into the vitreous, retinal traction and retinal detachment.

The severity of ROP is divided into stages and the location is divided into zones (International Committee for the Classification of Retinopathy of Prematurity, 2005). In stage 1, there is a marked line between vascularized and unvascularized retina. In stage 2, a ridge has formed and in stage 3, fibrous and vascular proliferations have developed. In stage 4 there is a subtotal retinal detachment and in stage 5, the detachment is total. Plus disease is a sign of severe ROP, encompassing dilation and increased tortuosity of the retinal vessels. ROP stage 2 is shown in Figure 1.

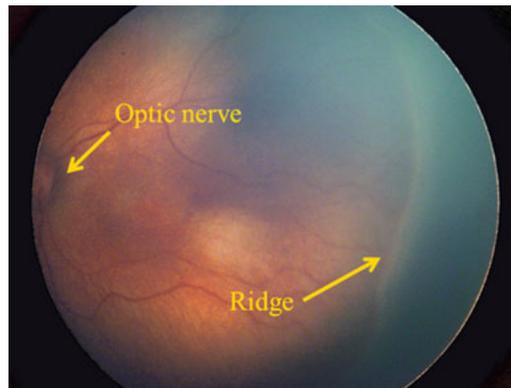


Figure 1. Retinopathy of prematurity (ROP) stage 2 in zone 2. (published with permission of the child's parents)

Today the treatment criteria for ROP in Sweden follow the recommendations of the ETROP study from 2003 (Good & Early Treatment for Retinopathy of Prematurity Cooperative, 2004). Standard treatment for ROP is laser photocoagulation of the unvascularized and ischemic retina behind the ROP border. Previously, cryotherapy applied in the same area was the method of choice. Anti-VEGF (vascular endothelial growth factor) substances injected in the vitreous are increasingly being used in eyes with severe or aggressive posterior ROP (Mintz-Hittner et al., 2011). The pharmacokinetic and long-term effects of these drugs are not fully known and how and when this treatment should be used is still controversial.

Today, guidelines for ROP screening are available in most countries (van Sorge et al., 2014; Wilkinson et al., 2009). In Sweden screening includes all

children born before 31 weeks of gestation and starts five weeks after birth or at gestational age 31 weeks at the earliest (Holmstrom et al., 2014b). Neonatologists are also recommended to refer older children with very low birth weight and/or who are severely affected by other diseases, for screening. Eye examinations are continued until any detected ROP has disappeared and/or the retina is fully vascularized.

Visual function in former preterm children

In recent years several large population-based studies on visual functions in former preterm children have been conducted, showing various visual dysfunctions (Hellgren et al., 2007; Holmstrom & Larsson, 2008; Jacobson et al., 2009). When children born at term were compared with former preterm children at school age the preterm children were found to have reduced visual acuity (Haugen et al., 2012; Larsson et al., 2005). Refractive errors including myopia, hyperopia and astigmatism are more common in prematurely-born children (Larsson et al., 2003). Strabismus, both exotropia and esotropia, is also more frequent in this group of children (Holmstrom et al., 2006; O'Connor et al., 2002). Contrast sensitivity is affected in prematurely-born children both with and without ROP (Larsson et al., 2006). Visual fields, however, only seem to be affected in preterm children who received treatment for severe ROP during the neonatal period or in those with neurological complications (Larsson et al., 2004). Visual fields in children with mild or no ROP do not differ from those in children born at term (Lindqvist et al., 2007).

In the EXPRESS study, a follow-up at 30 months showed that one third of the children had visual problems: low visual acuity, strabismus and significant refractive errors (Holmstrom et al., 2014a). In this group of extremely premature children the majority had ROP and one fifth were treated for the disease, which is one probable explanation for their visual dysfunctions. Other population-based follow-up studies of older children born less prematurely confirm these findings in children not as affected by ROP (Larsson et al., 2005). Further, visual problems can also be related to brain lesions due to the preterm birth such as IVH and PVL. Visual dysfunctions are also found in children with no evident neurological complications. Thus, affected visual functions in preterm children without any previous ROP and without known neurological complications, suggest an influence by the preterm birth per se on the retina and/or the visual pathways.

Retinal development

The retina is a complex structure containing many different cells in several layers, see Figure 2. The outer part of the retina consists of the photoreceptors that absorb the light entering the eye. Photoreceptors are divided into rods, which are activated by dim light, and cones, which require brighter light to function. The phototransduction cascade starts and the light is transformed to an electrical signal modified by the bipolar cells and conducted by the ganglion cells of the inner retina. The signal is transported through the retinal nerve fibers to the optical nerve and further through the visual pathway in the brain to the visual cortex where it is transformed into the image seen by us.

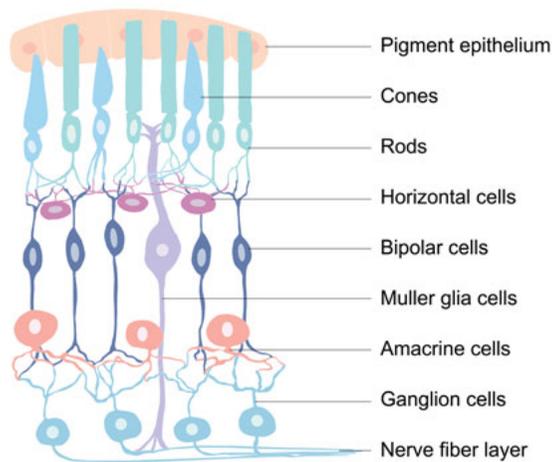


Figure 2. Schematic drawing of the retinal layers with the different retinal cells marked. (Illustration: Maria Ullbors)

Retinal development starts early after gestation and continues several years after birth (Wong, 2006). Soon after gestation the optic vesicles are formed from the neural crest and invagination of the vesicle forms the optic cup with two layers. The outer layer will form the retinal pigment epithelial layer and the inner layer is the origin of the neural retina. The different retinal cells begin to form from the 7th gestational week, starting with ganglion cells and cones and continuing with horizontal cells, amacrine cells and rods. Müller cells and bipolar cells are the last to develop. Around mid-gestation all retinal cells are present but still very immature (Hendrickson & Drucker, 1992).

The retina develops from the center to the periphery and the fovea, a region containing all retinal cell layers but only cone photoreceptors, can be identified as early as in the 10th to 11th week (Hendrickson, 1992). Around mid-gestation the foveal region consists of a thick layer of ganglion cells, a

thick inner nuclear layer and a single layer of thick, short, immature cones. Further development of the macular region can be divided into three major processes (Hendrickson et al., 2012). First, there is a movement of inner retinal cells from the center to the periphery creating the foveal depression. This development starts around a GA of 22 weeks and continues for several months after birth. Secondly, the cone photoreceptors start to migrate centrally and become more tightly packed together. This continues several years after birth and reduces the size of the foveal area considerably. The third important event is differentiation of the foveal cones. At 24-26 weeks of GA, the inner segments of the cones are visible, but it is not until the time of birth that the outer segments can be seen histologically. At birth, there is still only one layer of immature cones in the fovea and starting in the following months the cones elongate and become thinner. The elongation in combination with the central migration of the cones will create the multiple layers of cone photoreceptors seen in an adult foveal region. Cone differentiation seems to be the last part of macular development to be completed and it continues well into school age.

The peripheral retina develops later than the central retina and the peripheral rods later than the cones (Hendrickson & Drucker, 1992). Maturation of the photoreceptors, both cones and rods in the periphery is completed earlier than for the central cones and at birth the photoreceptors in the periphery are more mature than in the foveal region (Hendrickson et al., 2012).

The retinal ganglion cells start to form the RNFL and the optic nerve in the 8th gestational week (Taylor, 2005). A rapid increase in the number of ganglion cells occurs during the following 10 weeks, but at the end of this period apoptosis reduces the number of cells again and they are replaced with glia cells and collagen. During the last months of pregnancy the ganglion cells mature from the center to the periphery and at birth there are 1.1-1.3 million retinal ganglion cell axons in the optic nerve.

With new handheld devices the retinal morphology can be assessed by OCT in the neonatal period, providing us with more information about normal morphological development in the first years of life (Dubis et al., 2012). The OCT images seem to correlate well with anatomical structures seen in histological examinations.

Optical coherent tomography

OCT is a transpupillary technique that creates high-resolution cross-sectional images of the retina. The method uses low coherence near infra-red light, and by detecting the time delay in reflective, back scattered light, different retinal structures such as, nerve fiber layer thickness and total retinal thickness, can be described (Hee et al., 1995). To create an image, single scans, a-

scans, are merged together to create b-scans, and several b-scans are used to create a two-dimensional map of the macula, for example. To investigate the thickness of the retinal nerve fiber layer (RNFL), scans in a circle around the optic nerve head with a diameter of 3.4 mm have proven to give reliable results (Schuman et al., 1995).

The original OCT technique, time domain OCT (TD-OCT) uses six axial b-scans with the fovea in the center to create a map of the macula, where the areas between the b-scans are extrapolated by the instrument, see Figure 3A. TD-OCT is increasingly being replaced by a spectral domain technique (SD-OCT) that uses a Fourier transformation to simultaneously record all reflected light hence increasing the number of a-scans recorded (Wojtkowski et al., 2004). This makes the recording faster and provides a higher resolution and better visualization of retinal structures. In SD-OCT a macula map is created by scanning a 6 x 6 mm area and using the large number of a-scans obtained to create the same ETDRS map of the macula with much less extrapolation than in TD-OCT, see Figure 3B.

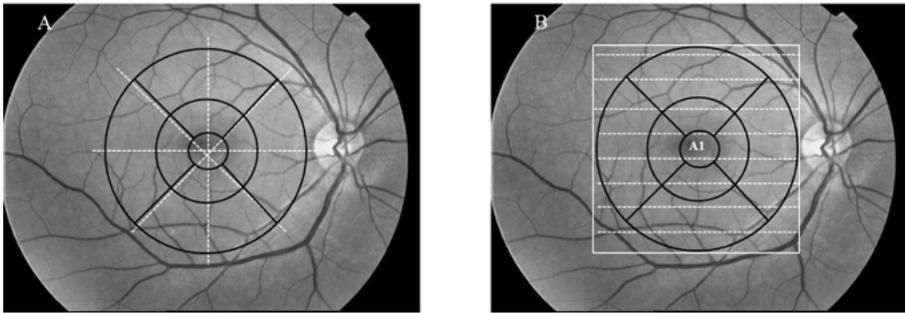


Figure 3. *A. Illustration of time domain OCT (TD-OCT) with axial scans (dotted lines) with the center in the fovea creating an ETDRS map. B. Illustration of spectral domain OCT (SD-OCT) which scans a 6 x 6 mm area over the macula and creates an ETDRS map. The central area A1 is marked.*

OCT is a fast, noninvasive and non-contact method, which makes it easy for most children to tolerate the procedure (Eriksson et al., 2009). Several population-based studies have used OCT to investigate of both macular thickness and RNFL thickness in large groups of healthy children from 6 years of age (Huynh et al., 2006; Luo et al., 2006). Repeatability of scans in healthy children is good and the intraocular difference is low (Eriksson et al., 2009).

Fullfield ERG

The fact that stimulation with light gives an electrical response from the retina has been known for more than hundred years. Frithiof Holmgren, the first Professor of Physiology at Uppsala University, demonstrated electrical fluctuations in the optic nerve of frogs, while stimulating the retina with light (Holmgren, 1865). During the following hundred-year period this discovery has developed into an important diagnostic tool for investigation of retinal function in the clinic as well as in research.

In ffERG the whole retina is stimulated with light of different color, intensity, frequency and time duration to get responses from different cell systems in the retina. It is possible to get responses from the rod photoreceptor system by dark-adapting the eye and then stimulating with low intensity light. When the intensity of the light is increased the response will be produced from both rods and cones, and with repeated stimulations with high intensity light the response will be produced only from cones. The International Society of Clinical Electrophysiology of Vision (ISCEV) has developed standards for performing ffERG (Marmor et al., 2009).

The ffERG response includes the a-wave, the first negative wave, and the b-wave, the first positive wave, and is described in Figure 4. There is also a c-wave and occillatory potentials, but these responses are not discussed further in this thesis. The a-wave of a dark adapted response is described as reflecting the photoreceptor function (Hood & Birch, 1990). The b-wave is believed to reflect the post-receptor cells, mainly bipolar cells. It has however been suggested that the early components of the post receptor response may affect also the a-wave (Robson & Frishman, 1998).

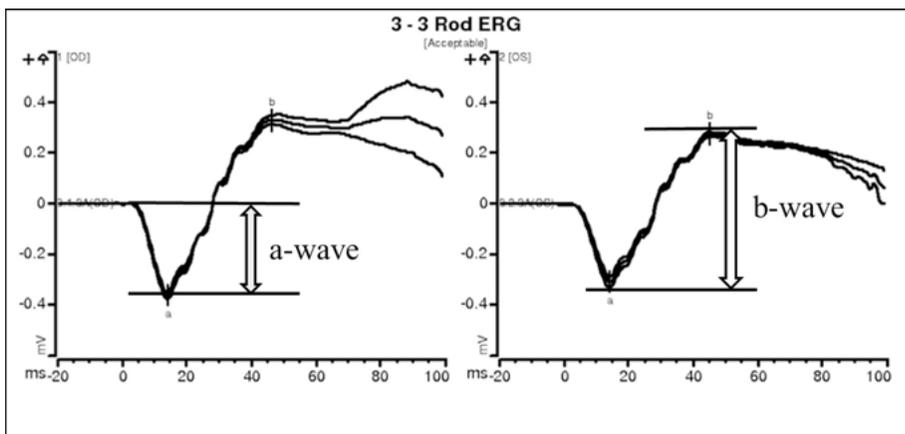


Figure 4. Dark-adapted combined rod/cone responses in fullfield ERG, in a normal subject. An a-wave and a b-wave are marked.

Various types of electrodes may be used in ffERG examinations; for example, contact electrodes, silver thread electrodes and gold foil electrodes. Different electrodes give the same waveform of the response but the amplitude differs (Bradshaw et al., 2004). This emphasizes how important it is for each research unit to develop its own normal material.

Multifocal ERG

MfERG, a much more recent technique, developed during the 1990s by Sutter and Tran, makes it possible to evaluate the function of localized areas of the retina (Sutter & Tran, 1992). In mfERG the central 40-50 degrees of the retina are stimulated by black and white hexagons repeatedly reversed in a pseudorandomized matter. Central fixation is important in order to get accurate results and various methods for controlling a steady fixation can be used. The ISCEV has developed standards for mfERG recordings (Hood et al., 2012). The ERG responses are recorded by electrodes as is done in ffERG and they are then calculated mathematically by cross correlation to obtain a response from each stimulated hexagon. The results are often presented in trace arrays as seen in Figure 5. The hexagons are scaled by eccentricity, smaller in the center and larger in the periphery, to get responses with approximately the same amplitude in all hexagons in normal subjects. The implicit time and amplitudes of N1, the first negative wave, and P1, the first positive wave, are often used for further calculations. The single responses can be averaged in areas, for example concentric rings, giving the average implicit time for the area and a density measure of the amplitude, where the sum of amplitudes is divided by the area in degrees. The results are often also presented in a scalar manner with color coding creating a color map as shown in Figure 5.

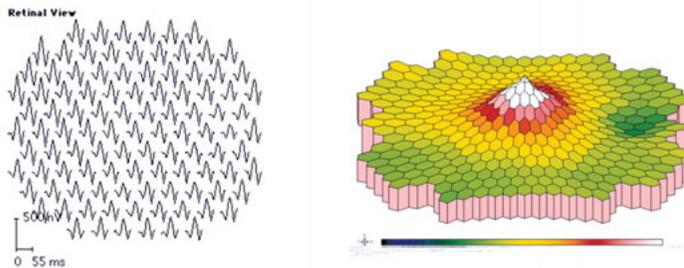


Figure 5. A trace array from a multifocal ERG, 103 hexagon protocol, in a healthy child and corresponding color coded map.

Aims

- To investigate macular morphology with OCT in prematurely-born children at school age and compare with results in children born at term (Paper I).
- To measure the peripapillar retinal nerve fiber layer thickness with OCT in former preterm children and compare with results in children born at term (Paper II).
- To evaluate total retinal function with ffERG in preterm children at school age and compare with results in children born at term (Paper III).
- To evaluate central macular function with mfERG in prematurely-born children and compare with results in healthy children (Paper IV).

Material

The study group in paper I and II included 68 children aged 5 to 16 year, who had been born at a GA of 32 weeks or less in Uppsala County. They had all been included in neonatal ROP screening at the Uppsala University Hospital. Their mean GA was 28.6 weeks (range: 22-32) and their mean BW was 1299 g (range: 453-2501). Thirty-six children had no ROP in the neonatal period, 23 children had mild ROP (stage 1-2) and 9 had severe ROP (stage 3-4), and five of those with severe ROP underwent cryotherapy or laser treatment.

The control group in paper I and II included 55 children aged 5 to 16 years who had been born at term ($GA \geq 37$ weeks), with normal birth weights ($BW \geq 2500$ grams) and normal visual acuity and refraction. (Eriksson et al., 2009) They were selected from the birth register of the Swedish National Board of Health and Welfare.

The study group in paper III included 35 former preterm children between 6 and 17 years of age, with the same background data as in papers I and II. The majority of the children had previously participated in the study presented in paper I and II. Their mean GA was 28.3 weeks (range: 22-32) and mean BW was 1225 g (range: 441-2470). Eighteen children had no ROP in the neonatal period, 12 children had mild ROP and 5 had severe and treated ROP. The control group consisted of 42 healthy children between 5 and 17 years of age, born at term with normal visual acuity.

The study group in paper IV included 15 former preterm children aged 9 to 17 years, who had been born before 32 weeks of gestation. The median GA was 30 weeks (range: 24-32) and the median BW was 1231 g (range: 611-2030). In this group 6 had no ROP, 7 had mild ROP and 2 had severe ROP that was treated during the neonatal period. All the children in the study group had previously participated in the studies of paper I-III. The control group consisted of mfERG results of 12 healthy children with normal visual acuity.

Methods

In all studies the best corrected VA was tested before giving the children dilating eye drops. Automatic refraction in cycloplegia and funduscopy were performed in all children.

OCT

In paper I and II the children were investigated with Stratus OCT 3, Version 4.0.1 (Carl Zeiss Meditec, Dublin, CA, USA). Macular thickness was measured with the “fast macular map protocol” which uses six radial scans with the fovea in the center. The results are presented in the nine ETDRS areas, where A1 is the central 1-mm circle. RNFL thickness was assessed with the “optic nerve head program” which makes 512 a-scans in a circle with a diameter of 3.4 mm around the optic nerve head. Right and left eyes of the premature group were compared with randomized eyes in the control group.

In paper IV the preterm children were examined with the SD-Cirrus HD OCT 4000 (Carl Zeiss Meditec, Dublin, CA, USA). The “macular cube 512 x 128” was used to scan an area of 6 x 6 mm of the posterior pole. The retinal thickness results are presented in the nine ETDRS regions.

Fullfield ERG

In paper III the children were examined with ffERG using the Espion system (Diagnosys LLC, Lowell, MA, USA). Reference electrodes were placed on both cheeks and Dawson-Trick-Litzkow- (DTL-) electrodes were placed at the edge of the lower eyelid in both eyes. A ground electrode was placed on one hand and an impedance of 7 k Ω was accepted. After dark adaptation for twenty minutes the children were placed in a Ganzfeld dome and the retina was stimulated with light flashes produced by white flash LED-s with different intensity and duration. The first four stimulations were performed in the dark to get isolated rod responses as well as combined rod/cone responses. The last two stimulations were performed in room light with bright flashes to get isolated cone responses. Details of the ERG protocol can be seen in Table 1. The stimulations were in accord with ISCEV standard with the exception of the exclusion of light adaptation time to make it easier for the children

to tolerate the examination (Marmor et al., 2009). Amplitudes and implicit times of a-waves and b-waves of the different responses were recorded.

Table 1. Description of the protocol for fullfield ERG according to light intensity, background light and type of response.

Response name	Light intensity (cd/s/m ²)	Dark adapted	Background light (cd/m ²)	Type of response
Rod 0.009	0.009	Yes	None	Rod
Rod 0.17	0.17	Yes	None	Rod/cone
Rod 3.0	3.0	Yes	None	Rod/cone
Rod 12.0	12.0	Yes	None	Rod/cone
30 Hz flicker	3.0	No	34.0	Cone
Single cone flash	3.0	No	34.0	Cone

Multifocal ERG

In paper IV mfERG was recorded using the Visual Evoked Response Imaging System (VERIS 6 EDI, San Mateo, CA, USA). After topical anesthesia was administrated in the eye a Burian-Allen bipolar contact lens was applied on the cornea of one eye and a ground electrode was placed on the forehead. A protocol with 103 black and white hexagonal elements, displayed in a cathode ray tube (CRT) monitor, was used. Stimulation parameters were in accordance with ISCEV recommendations (Hood et al., 2012). Fixation was continuously monitored with an infrared eye camera using infrared light at the edge of the corneal electrode to illuminate the fundus.

Results from right eyes in the preterm group and right or left eyes in the control group were used for comparing the two groups. The amplitudes and implicit times of the first order component P1 were analyzed, and the results were presented in five concentric rings.

The 6 mm in diameter ETDRS map of the OCT approximately corresponds to the four innermost concentric circles (14°) of the mfERG and the central ETDRS area (A1) corresponds to the central ring of the mfERG (4°) as described in Figure 6 (Holm et al., 2007).



Figure 6. Schematic description of the 103 hexagon protocol of the multifocal ERG. Rings 1-5 are marked in colors, ring 1=red to ring 5=blue. The ETDRS map of the OCT is marked in black. (Illustration: Maria Ullbors)

Statistical methods

In paper I the preterm and control groups were compared using independent t-tests and one-way ANOVA. Pearson's test for bivariate correlation and multiple linear regressions were used to analyze the relationship between macular thickness and other variables such as GA, BW and VA.

In paper II the preterm and control groups were compared using the Mann-Whitney U test and the Kruskal-Wallis test followed by Dunn's multiple comparison test. To investigate the effect of age, an ANCOVA model was used to compare the four groups. Pearson's test for bivariate correlation and multiple linear regressions were used to analyze the relationship between RNFL thickness and variables such as GA, BW and VA.

In paper III and IV the preterm and control groups were compared using the Mann-Whitney U test. In the preterm groups correlations between ffERG and mfERG responses and variables, such as GA and VA, were analyzed with Spearman's test. Non-parametric testing was used throughout in accordance with ISCEV recommendations (Hood et al., 2012).

Results

Paper I

Sixty-five preterm children and 55 fullterm children completed the macula OCT investigation. The macula was significantly thicker in the most central area, A1, in the prematurely-born children compared to children born at term. There were no differences between the groups regarding the other areas or the total macular volume, see Figure 7.

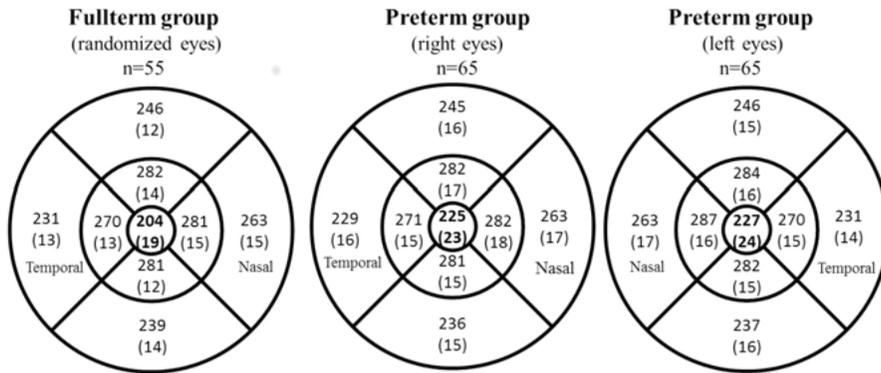


Figure 7. Macular thickness measured with OCT in the nine ETDRS areas, mean (SD), in the fullterm group, randomized eyes, preterm group, right eyes and preterm group, left eyes.

In the preterm group, the central macula was significantly thicker in the children with previous ROP than in the children without ROP.

In a multiple regression analysis, including GA, BW, ROP (yes/no), neurological complications, age at examination, gender and VA, low GA at birth was the major risk factor for a thick central macula. There was no correlation between central macular thickness and visual acuity.

For illustration, Figure 8 shows the OCT image of one of the thickest maculae in the preterm group in comparison with the OCT image from a child in the control group.

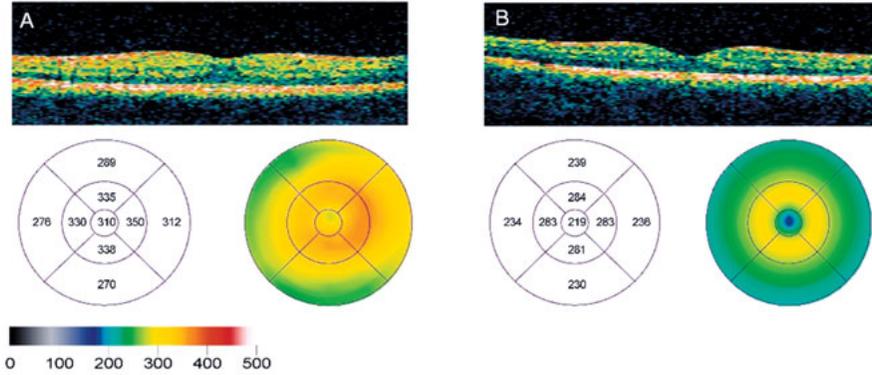


Figure 8. Macula map measured with time domain OCT **A.** Preterm child. **B.** Child born at term.

Paper II

OCT measurements of the RNFL could be completed in 62 preterm children and 54 controls. The RNFL thickness was significantly thinner in the superior and nasal quadrants in the children born prematurely compared to children born at term, as was the average RNFL thickness. The difference between the groups was mainly due to the group of children with severe ROP or severe ROP that was treated, see Figure 9.

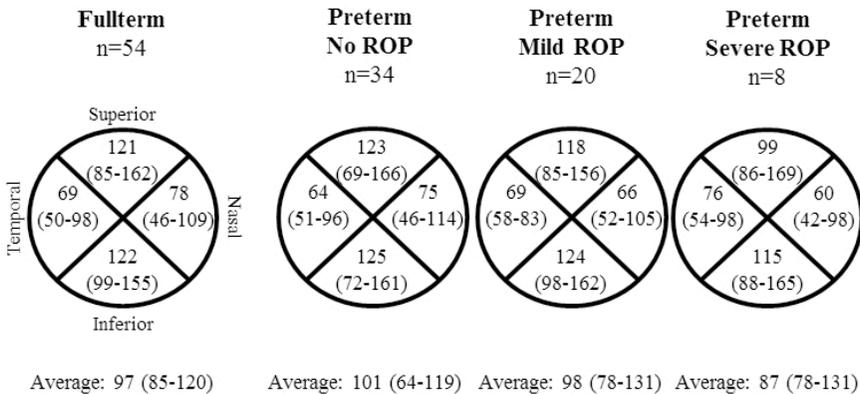


Figure 9. Median and range of retinal nerve fiber layer (RNFL) thickness (um) in the superior, nasal, inferior, temporal quadrants and average thickness for the fullterm group (randomized eyes) and the preterm group (right eyes) divided into groups according to stages of ROP.

The difference remained when excluding the children with known neurological complications from the analysis.

In the preterm group average RNFL thickness increased with larger BW. There was no significant correlation between RNFL thickness and VA, refraction or GA in the preterm group.

Paper III

All children in both groups were able to complete the ffERG investigation and results from right eyes were used in the analysis. Former preterm children had reduced a-wave amplitudes in the dark-adapted combined rod/cone responses, Rod 0.17, Rod 3.0, and Rod 12.0, compared to children born at term. There were no differences between the groups regarding a-wave implicit times in any of these responses or regarding b-wave amplitudes or implicit times. Amplitudes and implicit times for the a-waves of the combined rod/cone responses are described in Table 2. Regarding the cone responses, 30 Hz flicker and single cone flash, there were no difference between the preterm- and fullterm groups regarding either implicit times or amplitudes.

Table 2. Median and range of implicit times and amplitudes for the a-wave of full-field ERG dark-adapted rod/cone responses, Rod 0.17, Rod 3.0 and Rod 12.0.

ffERG response	Fullterms n=42	Preterms n=35	p-value
Rod 0.17			
Implicit time (ms)	25.8 (23.5-31.5)	25.5 (23.5-27.0)	0.556
Amlitude (uV)	99.4 (46.6-292.7)	79.3 (22.4-214.4)	0.022
Rod 3.0			
Implicit time (ms)	15.0 (13.5-16.0)	15.0 (14.0-16.0)	0.468
Amplitude (uV)	280.6 (131.0-446.4)	195.1 (115.6-358.8)	0.003
Rod 12.0			
Implicit time (ms)	11.5 (10.0-14.0)	12.0 (10.0-14.5)	0.251
Amplitude (uV)	314.1 (131.8-532.2)	237.9 (51.6-441.8)	0.000

When the preterm group was divided into two groups, preterms without ROP and preterms with ROP, multiple comparisons showed that the difference between fullterm and preterm children was mainly due to the difference between fullterms and the preterms with ROP. There was a difference between the fullterm group and the preterms without ROP and between preterm with and without ROP, as described in the box-plots in Figure 10, but the differences were not statistically significant.

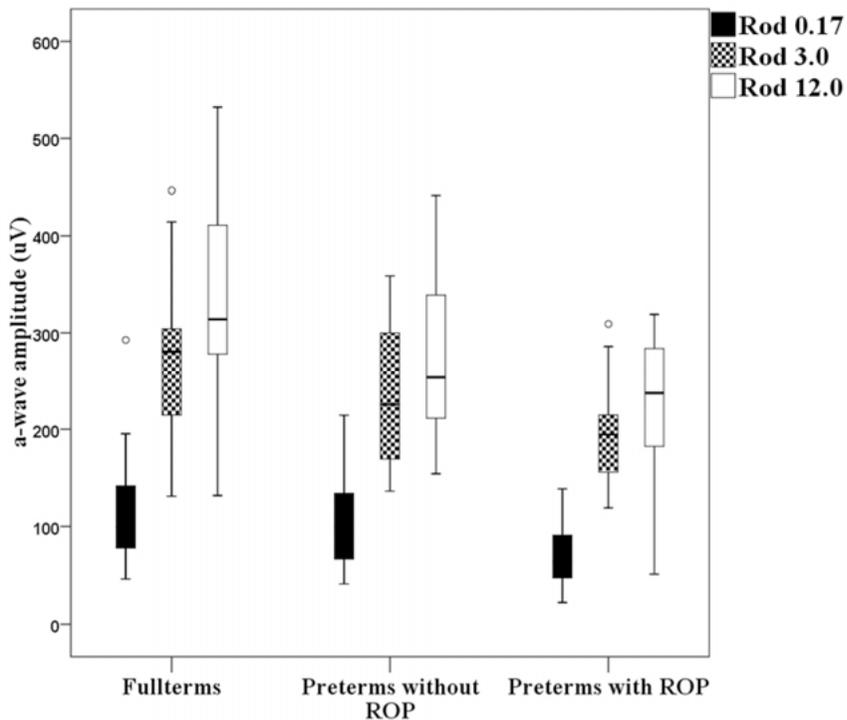


Figure 10. *A-wave amplitude in Rod 0.17, Rod 3.0 and Rod 12.0 responses in right eyes of the fullterm group, the preterms without ROP and the preterms with ROP. Each box show the median and interquartile range, bars show range and circles outliers.*

Paper IV

All 15 preterm children were able to complete the mfERG. The P1 amplitudes in Ring 1-5 were significantly reduced in the preterm group compared to the control group. The P1 implicit times were prolonged in the preterm group but the difference compared to the controls was not significant. P1 amplitudes and implicit times in Rings 1-5 are presented in Table 3.

Table 3. P1 implicit times and amplitudes in Rings 1-5 of the multifocal ERG in the control group and the preterm group.

	Controls n=12	Preterms n=15	p-value
Implicit time (ms)			
Ring 1	27.9 (25.8-30.0)	29.2 (25.0-30.8)	0.26
Ring 2	27.1 (25.0-29.2)	28.3 (24.2-30.0)	0.14
Ring 3	26.7 (25.0-28.3)	27.5 (23.3-30.8)	0.18
Ring 4	26.7 (25.0-29.2)	28.3 (24.2-29.2)	0.26
Ring 5	27.1 (25.0-30.8)	28.3 (25.0-30.0)	0.50
Amplitude (nV/deg²)			
Ring 1	40.7 (21.7-51.4)	27.6 (10.1-45.5)	0.01
Ring 2	27.9 (16.3-35.8)	19.1 (7.6-31.4)	0.02
Ring 3	22.8 (12.9-29.6)	16.5 (6.3-24.2)	0.02
Ring 4	18.7 (11.0-26.3)	13.9 (6.0-20.0)	0.01
Ring 5	16.9 (10.3-25.6)	11.9 (5.5-18.5)	0.01

There was a positive correlation between P1 implicit time in Ring 1 and central macular thickness in A1, as measured with OCT, in the right and left eyes of the preterm group. See Figure 11.

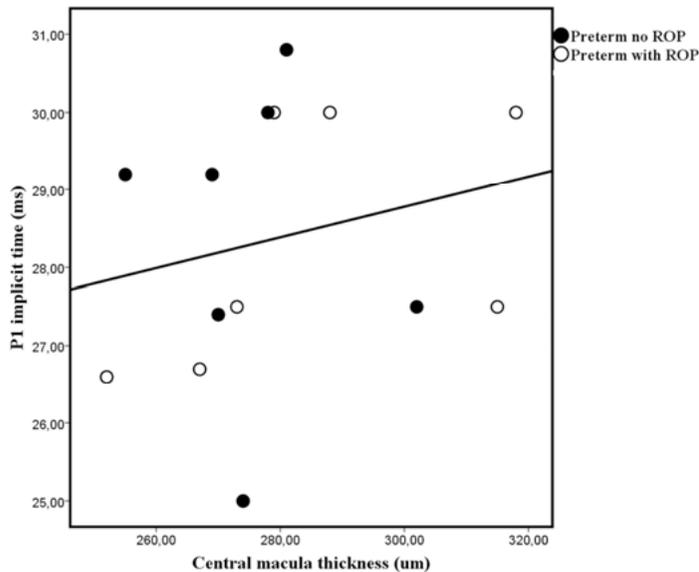


Figure 11. Relation between central macular thickness in A1 measured with OCT and P1 implicit time in Ring 1 of multifocal ERG in right eyes in the preterm group.

Discussion

Macular morphology and function. (Paper I and IV)

In this thesis different aspects of retinal structure and function in former preterm children have been evaluated. Children born preterm had a thicker central macula compared to fullterm children when measured at school age. Similar results have been reported by Recchia et al. and Ecsedy et al. (Ecsedy et al., 2007; Recchia & Recchia, 2007). Both these studies and our study used TD-OCT for measurements of retinal thickness, thereby not allowing for a more detailed evaluation of the different retinal layers. Later studies with SD-OCT have shown that there seems to be a persistent inner retinal layer that causes the increased thickness and that the outer retinal layer is intact (Villegas et al., 2014; Wu et al., 2012). In the normal development of the macular region the inner retinal layer is supposed to move towards the periphery to form the foveal dimple during the second part of gestation (Hendrickson & Yuodelis, 1984). The persistent layer suggests that a preterm birth disturbs this process. Future studies on adults with a history of preterm birth will reveal if this persistent layer is actually something that remains and not only an expression of a delayed maturation.

MfERG is a method to determine the function of the macula and in paper IV we could show a reduction of the amplitude in the P1 response which suggests a reduced function in former preterm children when compared to healthy controls. Fulton et al. also showed reduced amplitudes and prolonged implicit times in former preterm children with mild ROP. Although both studies are small, they indicate that not only macular morphology, but also macular function is affected (Fulton et al., 2005).

Macular diseases including diabetic retinopathy and macular degeneration also affect the mfERG response with reduced amplitudes and prolonged implicit times (Garcia-Garcia et al., 2013; Holm et al., 2007). ROP is a retinal disease that affects the retinal vessels and leads to retinal ischemia. Hand-held OCT devices have made it possible to investigate the macula in both preterm and fullterm infants. It has been shown that preterms with ROP have macular changes in the neonatal period including macular edema and subretinal fluid, not unlike changes seen in diabetic retinopathy (Dubis et al., 2013). Even if these changes resolve with time, it is not known how they affect function later in life, and if children with macular changes early in life may have affected mfERG responses later.

In paper IV we found a positive correlation between P1 implicit time in the most central ring of the mfERG and the thickness of the central area of the macula measured with OCT. Using SD-OCT, Vajzovic et al. recently showed that preterm infants have a delayed development of the photoreceptor area in the central macula (Vajzovic et al., 2015). It is possible that this delay results in a persistent reduced function of the photoreceptors in line with the unfinished development of the macular region seen in prematurely-born children.

Retinal nerve fiber layer thickness. (Paper II)

Prematurely-born children with severe ROP and ROP that required treatment, had reduced RNFL thickness compared with preterm children with no or only mild ROP, and compared with children born at term. These results were confirmed in a recent study by Pueyo et al. who also reported an effect on the RNFL only in premature children treated for ROP (Pueyo et al., 2015).

Neurological complications affecting the white matter of the brain, like IVH and PVL, are common in the neonatal period in very preterm children. Children with this kind of brain damage have been found to have increased cupping of the optic nerve, and it has been suggested that retinal ganglion cells can be affected by retrograde degeneration (Jacobson et al., 2009). In a recent study of adults with known white matter damage in the neonatal period, Lennartsson et al. described a large reduction in peripapillary RNFL thickness which confirms earlier findings (Lennartsson et al., 2014). In our study however, there were few children with known neurological complications and when comparing that group of children with preterm children with no known neurological complications, there was no difference in RNFL thickness.

Standard treatment of severe ROP at the time the children in our study were born was cryotherapy or laser treatment of the peripheral retina. This treatment is similar to the panretinal photocoagulation (PRP) used in patients with proliferative diabetic retinopathy. Several studies have shown a reduction in peripapillary RNFL thickness after PRP (Kim et al., 2012; Lim et al., 2009). This suggests that the treatment damages the ganglion cells and reduces their number, which can be in line with the results of our study. Patients with severe diabetic retinopathy but who are not treated with PRP also have reduced RNFL suggesting damage to ganglion cells by the disease itself (Park et al., 2011). It is possible that the same process could explain the reduced RNFL thickness in children with severe ROP that did not need treatment.

In the present study a low BW was correlated with a thinner RNFL. This has also been shown by Wang et al. in a large population-based study of 6-

year-old children, where children with a BW lower than 2500 g had a thinner RNFL than children with normal BW (Wang et al., 2006). In an earlier study Wikstrand et al. described a smaller rim area of the optic nerve in preterm children and a correlation with low BW and poor postnatal growth (Wikstrand et al., 2010). Since the maturation of retinal ganglion cells and the formation of the optic nerve take place during the second part of gestation, it seems likely that a low birth weight would affect the normal development of the retinal ganglion cells.

Total retinal function (Paper III)

Total retinal function can be evaluated with fullfield ERG and in paper III we described how photoreceptor function was reduced in preterm children compared to children born at full term. The reduction was evident in the dark-adapted combined rod/cone responses but not in the isolated cone response, indicating that rods are more affected than cones. Fulton et al. has described reduced rod sensitivity and saturation in preterm children both as infants and at school age, which is in line with our results (Fulton et al., 2001; Harris et al., 2011). In the peripheral retina, photoreceptors include both rods and cones but their development differs. Rods mature later than peripheral cone photoreceptors, which can explain why they are more affected by a preterm birth (Hendrickson et al., 2008). ROP is one known risk factor for reduced rod photoreceptor function but in paper III preterm children without ROP also had a tendency towards reduced rod response, suggesting that prematurity per se can have an effect on the normal development of photoreceptors. Future studies including more children without ROP could elucidate this further.

Conclusion

In conclusion retinal morphology and function are affected in several different ways in prematurely born children. Some of the changes are due to ROP and to treatment of the disease and some are probably due to prematurity per se. None of the retinal changes presented in this thesis were correlated with reduced visual acuity in the preterm group, which could be surmised. This can have several explanations. Firstly, changes in the retina are only one part of a more complex explanation. For example, subtle changes in the visual pathway and brain in preterm children may play a part. Secondly, the way in which visual acuity is measured is inexact and more precise techniques than those available today would be needed to detect more subtle changes in visual acuity. However, our increased knowledge of retinal morphology and function in these children contributes to the understanding of how their vision works, see Figure 12. In the future we will hopefully better understand the mechanisms underlying these changes and how we can care for prematurely-born children during the neonatal period to avoid the visual dysfunctions we see today.

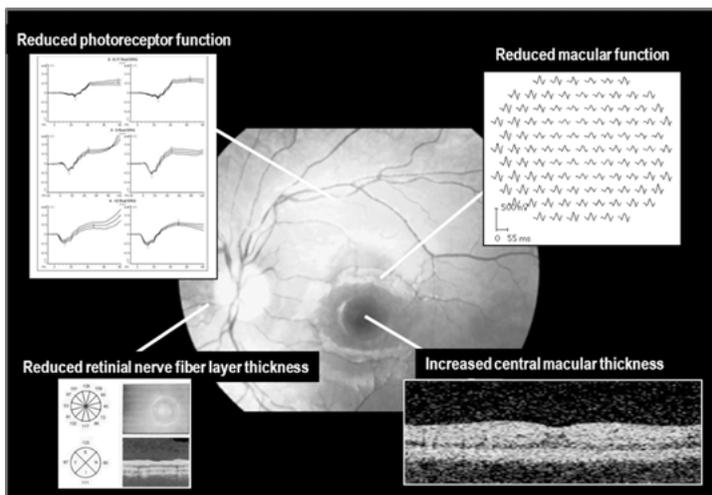


Figure 12. A summary of changes in retinal morphology and function in former preterm children.

Sammanfattning på svenska

Prematur födelse innebär att ett barn föds före 37:e graviditetsveckans utgång och idag är det inte helt ovanligt att barn föds så tidigt som i 22:a graviditetsveckan. Överlevnaden hos dessa extremt prematura barn har ökat, vilket beror på förbättrad vård både i anslutning till födelsen och under neonatalperioden. För tidig födsel innebär, framför allt för de allra minsta barnen, en stor risk för komplikationer under den första levnadstiden. Ögonen kan drabbas av retinopathy of prematurity, ROP, som är en näthinnesjukdom som drabbar de minsta och sjukaste barnen. Den omogna näthinnans tillväxt störs vilket ger en syrebrist som i sin tur kan leda till kärlnybildningar. Dessa nybildade kärl blöder lätt och kan också växa ut i glaskroppen och orsaka en dragning i näthinnan, vilket kan leda till en näthinneavlossning och i värsta fall blindhet. För att förhindra detta screenas alla barn födda före 31:a graviditetsveckan och vid tecken på allvarlig ROP behandlas näthinnan med laser.

Allvarlig ROP är en välkänd orsak till nedsatt synfunktion hos för tidigt födda barn när de växer upp, men även barn utan ROP under neonatal perioden kan ha besvär med synen. Det är vanligare med subnormal synskärpa, skelning och glasögonbehov hos prematurfödda barn än hos fullgångna barn. Studier har också visat att synfält och kontrastseende kan vara påverkade.

Ögats utveckling startar tidigt men näthinnan utvecklas till stor del under den andra delen av graviditeten och är långt ifrån färdigutvecklad då de prematura barnen föds. I denna avhandling ingår fyra arbeten där näthinnans morfologi och funktion har undersökts med olika tekniker för att kunna avgöra vilka effekter en för tidig födelse har.

Näthinnan kan undersökas med optical coherence tomography, OCT, som med hjälp av reflekterat ljus kan visualisera näthinnans olika skikt och ger möjlighet att mäta näthinnans tjocklek och se avvikelser i strukturen.

Näthinnans funktion kan mätas med elektroretinografi, ERG, där stimulering av näthinnan med ljus av olika intensitet, frekvens eller mönster genererar ett svar som registreras med elektroder, se Figur 13. Med hjälp av s.k. fullfält-ERG (ffERG) mäts hela näthinnans funktion och med multifokalt ERG (mfERG) mäts den centrala näthinnefunktionen.

I de arbeten som ingår i avhandlingen undersöktes barn i åldrarna 5-19 år som var födda före 32:a graviditetsveckan. Som kontrollgrupp undersöktes barn i samma åldrar som var födda efter fullgången graviditet och hade normal synskärpa. I arbete I och II undersöktes näthinnan med OCT.



Figur 13. Ett av de barn som ingick i kontrollgruppen i arbete III, uppkopplad med elektroder som mäter näthinnans funktion. (Publicerad med tillstånd av vårdnadshavare och barn)

Den centrala delen av näthinnan, macula eller gula fläcken, visade sig vara tjockare i centrum hos de för tidigt födda barnen. Däremot visade sig tjockleken av retinala nervfibrerlagret runt synnerven vara tunnare i prematurgruppen, framför allt hos de barn som haft svår ROP eller blivit behandlade för ROP. I arbete IV undersöktes den centrala näthinnans funktion med mfERG och resultatet visade sämre funktion i prematurgruppen än i kontrollgruppen. Undersökning av hela näthinnans funktion utfördes med fFERG i arbete III och den visade en påverkan på fotoreceptorernas funktion i prematurgruppen.

Sammanfattningsvis visar resultaten i arbete I-IV att både näthinnans struktur och funktion påverkas av för tidig födelse. Studierna visade inte något samband mellan näthinneförändringarna och synskärpa hos de för tidigt födda barnen, vilket kan bero på flera faktorer. För det första är synskärpan eventuellt ett för grovt mått på synfunktionen och en känsligare metod skulle behöva utvecklas. För det andra kanske näthinneförändringarna bara är en del i en mer komplex förklaring till varför för tidigt födda barn har nedsatt synfunktion när de växer upp. Fortsatta studier på både barn och vuxna med nyare, finare tekniker kommer kunna ge mer information om hur och varför näthinnans funktion påverkas av för tidig födelse. Förhoppningsvis kan resultaten i dessa arbeten, tillsammans med framtida forskning, hjälpa till att hitta metoder och behandlingar för att förhindra näthinneförändringar som leder till nedsatt synfunktion hos för tidigt födda barn.

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